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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/668,073	09/19/2003	Andrew H. Segal	11111/2003F	3004

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EXAMINER	
BLUMEL, BENJAMIN P	

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1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/668,073	SEGAL ET AL.	
	Examiner	Art Unit	
	BENJAMIN P. BLUMEL	1648	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-82* is/are pending in the application.

4a) Of the above claim(s) *5-9, 13, 14 and 40-78* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,10-12,15-39 and 79-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants are informed that the rejections of the previous Office action not stated below have been withdrawn from consideration in view of the Applicant's arguments and/or amendments.

Election/Restrictions

Claims 5-9, 13, 14 and 40-78 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on December 21, 2006.

Claims 1-4, 10-12, 15-39 and 79-82 are examined on the merits.

Response to Arguments

Applicant's arguments with respect to claims 1-4, 10-12, 15-39 and 79-82 have been considered but are moot in view of the new ground(s) of rejection. However, some of the previously cited references are still applied below with corresponding responses by the Examiner.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

(New Rejection) Claims 1-3, 10-12, 30-34, 36, 37 and 39 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 and 10-16 of copending Application No. 10/667,193 in view of Hoo (US 5,891,432).

The co-pending invention is drawn to a method of modulating an immune response in a mammal/human by administering a composition containing an antigen bearing target (cell or virus) and a multi-functional molecule containing a first amino acid sequence of a cell-surface binding moiety and a second amino acid sequence comprising a ligand for a cytokine receptor (GM-CSF). The multi-functional molecule is a fusion polypeptide wherein the first amino acid sequence is N-terminal or C-terminal to the second amino acid sequence. The ligand is specific for a mouse cell surface polypeptide, such as leukocytes, professional antigen presenting cells, such as dendritic cells. The multi-functional molecule can be bound or unbound to the antigen bearing target. Therefore, in view of Hoo who teaches the generation of a multi-functional molecule with a naturally occurring lectin fused with murine GM-CSF, the co-pending invention is an obvious variant of the instant one.

This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(New Rejection) Claims 1-3, 10-12, 17, 27, 28, 30-36, 81 and 82 are rejected under 35 U.S.C. 102(b) as being anticipated by Hoo (US 5,891,432) as evidenced by Erbe et al. (Journal of Cell Biology, 1993) and Cantrell et al. (PNAS, 1985).

The claimed invention is drawn to a method of modulating an immune response in a mammal/human by administering a composition containing an antigen bearing target and a multi-functional molecule containing a first amino acid sequence of a naturally occurring lectin and a second amino acid sequence comprising a ligand for a cytokine receptor. The multi-functional molecule is a fusion polypeptide wherein the first amino acid sequence is N-terminal or C-terminal to the second amino acid sequence. The ligand is specific for a mouse cell surface polypeptide, such as leukocytes, professional antigen presenting cells, such as dendritic cells. The multi-functional molecule can be bound or unbound to the antigen bearing target. It is noted that on page 2 of the specification, "an "antigen bearing target" is an entity which comprises an antigen. As used herein an "antigen bearing target" includes, for example, a whole cell which expresses an antigen a cell fraction comprising an antigen, a membrane fraction comprising an antigen, a virus comprising an antigen, a viral particle comprising an antigen, or an antigen, e.g. a polypeptide antigen, which may be free of any other cell-derived or virus-derived material. Cellular fractions may be prepared using methods known to those of skill in the

art such as those taught in Cell Biology A Laboratory Handbook (Academic Press 1994 Editor J. E. Celis ISBN 0-12-164715-3)."

Hoo teaches the use of antigen bearing targets, such as cells that express a fusion polypeptide based on one amino acid sequence of P-selectin fused with either a second amino acid sequence of murine GM-CSF or IL-2. The P-selectin employed (a natural lectin) inherently has a carbohydrate binding domain as evidenced by the teachings of Erbe et al. In addition, the murine GM-CSF used contains at least five contiguous amino acids which the human form also contains as evidenced by Cantrell et al. and that professional APCs, such as dendritic cells, contain receptors for GM-CSF. Hoo also teaches that the fusion polypeptides can be formed by fusing the lectin to the N- or C-terminus of the GM-CSF peptide and that the fusion polypeptide can be either attached or unattached to the antigen bearing target (i.e., cell). Therefore, Hoo anticipate the claimed invention as evidenced by Erbe et al. and Cantrell et al.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

(New Rejection) Claims 1-4, 10-12, 15, 16, 18-39, 81 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoo *supra*, Erbe et al.*supra*, Cantrell et al. *supra*, Faulkner et al. (International Immunology, 2001), Operschall et al. (Journal of Clinical Virology, 1999) and Nobusawa et al. (Virology, 1991).

The claimed invention is drawn to a method of modulating an immune response in an animal with a 10 amino acid fragment of influenza hemagglutinin (HA) fused with a ligand for a cytokine receptor. The animal could be a mammal, such as a human.

Additionally, the HA fragment is of the influenza virus A/PR/8/34 and is N-terminal to the ligand. The HA, a naturally occurring Lectin, is capable of binding to a carbohydrate structure with sialic acids. The claimed invention also involves an influenza virus hemagglutinin H2 or H3 or a HA of an influenza that does not infect humans. In addition, the ligand is mouse or human GM-CSF and is fused with the HA antigen at the N- or C-terminus of GM-CSF. It is noted that on page 2 of the specification, "an "antigen bearing target" is an entity which comprises an antigen. As used herein an "antigen bearing target" includes, for example, a whole cell which expresses an antigen a cell fraction comprising an antigen, a membrane fraction comprising an antigen, a virus comprising an antigen, a viral particle comprising an antigen, or an antigen, e.g. a polypeptide antigen, which may be free of any other cell-derived or virus-derived material. Cellular fractions may be prepared using methods known to those of skill in the art such as those taught in Cell Biology A Laboratory Handbook (Academic Press 1994 Editor J. E. Celis ISBN 0-12-164715-3)."

The teachings of Hoo are summarized above, however Hoo does not discuss the use of influenza hemagglutinin as the lectin.

The teachings of Erbe et al. are discussed above.

The teachings of Cantrell et al. are discussed above.

Faulkner et al. teach the development of a chimeric vaccine comprising 10 amino acid region of HA from Influenza virus A/PR/8/34 (PR8) linked to IL-2 and the importance of researching other chimeric cytokine-antigen vaccines that provide the therapeutic effects of the cytokine with the antigenic properties of the antigen in addition to improving the half-life of the cytokine *in vivo*. Some examples of cytokine candidates

are IFN-γ, GM-CSF, IL-4, and IL-10 since the respective receptors are expressed by Dendritic Cells (DCs), which also function as antigen presenting cells, as also discussed by Faulkner et al. Faulkner et al. further teach the use of the HA-IL-2 chimeric in the activation of bone marrow-derived dendritic cells with compared to treatments with separated HA and IL-2. Even though did not administer the chimeric vaccine to an animal, Faulkner et al. observed an increased T cell activation by way of antigen presentation of the chimeric composition from DCs and they also disclose that previous studies pertaining to *in vivo* activity of similar chimeras have been analyzed.

Operschall et al. teach the co-administration of plasmid DNA that encodes Influenza A/PR/8/34 hemagglutinin and mouse GM-CSF to mice in order to protect against viral infection. Operschall et al. observed that the cytokine-antigen combination possess adjuvant properties.

Nobusawa et al. teach the comparison of 13 HA serotypes of Influenza A viruses. In particular, Nobusawa et al. H2, H3, H8 and H12, of which, H8 and H12 serotype viruses are not known to have infected humans as of yet.

It would have been obvious to one of ordinary skill in the art to modify the methods taught by Hoo (and evidenced by Erbe et al. and Cantrell et al.) and Faulkner et al. in order to link hemagglutinin from PR8 to GM-CSF as part of immunogenic composition also containing an antigen bearing target as discussed above. One would have been motivated to do so, given the suggestion by Hoo and Faulkner et al. that the method be used to produce fusion polypeptides with lectins fused to cytokines, particularly using influenza HA and GM-CSF. There would have been a reasonable expectation of success, given the knowledge that the co-administration of influenza HA

and mouse GM-CSF have adjuvant related properties, as taught by Operschall et al., and also given the knowledge that various Influenza A hemagglutinin antigens (H2, H3, H8 and H12) are known based on sequence analysis, as taught by Nobusawa et al. Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Responses:

Applicants argue that Faulkner et al. do not teach the claimed antigen bearing target in conjunction with the multi-functional molecule of a carbohydrate binding HA fused to GM-CSF. Applicants also argue that Faulkner et al. do not teach a vaccine comprising the above mentioned composition being administered. In response, it is acknowledged that Faulkner et al. do not teach the exactly claimed composition. With regard to the statement pertaining to the lack of Faulkner et al. to teach a vaccine comprising the same, such a limitation is not claimed at this point, therefore Faulkner et al. do not need to teach a vaccine. Furthermore, Faulkner et al. do teach how to make a fusion polypeptide containing an influenza PR8 HA segment linked to IL-2 which can be used to activate dendritic cells.

Applicants further argue that the teachings of Faulkner et al. do not suggest to substitute their HA fragment with a sialic acid binding domain of HA and if they did, one would expect the binding affinity to inhibit the interaction between the GM-CSF and its cellular receptor. However, even though Hoo employ a different lectin than Faulkner et al. he is able to effectively use the multi-functional fusion polypeptide without inhibiting the GM-CSF activity.

Applicants argue that Operschall et al. do not teach the fusion construct of influenza HA and GM-CSF, only dual plasmid immunization. In response, it is acknowledged that Operschall et al. do not teach the claimed fusion polypeptide, but they do teach the adjuvant effects that expressed GM-CSF and influenza HA have on protecting mice from influenza infections.

(New Rejection) Claims 1-3, 10, 79 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoo *supra*, Erbe et al.*supra*, Cantrell et al. *supra*, Guillett et al. (European Journal of Biochemistry, 2002), Robinson et al. (Proceedings of the National Academy of Science, 1998).

The claimed invention is drawn to a method of modulating an immune response in a mammal/human by administering a composition containing an antigen bearing target and a multi-functional molecule containing a first amino acid sequence of a naturally occurring lectin and a second amino acid sequence comprising a ligand for a cytokine receptor. The multi-functional molecule is a fusion polypeptide wherein the first amino acid sequence is N-terminal or C-terminal to the second amino acid sequence and are linked through a Glycine-Serine linker. The ligand is specific for a mouse cell surface polypeptide, such as leukocytes, professional antigen presenting cells, such as dendritic cells. The multi-functional molecule can be bound or unbound to the antigen bearing target. It is noted that on page 2 of the specification, "an "antigen bearing target" is an entity which comprises an antigen. As used herein an "antigen bearing target" includes, for example, a whole cell which expresses an antigen a cell fraction comprising an antigen, a membrane fraction comprising an antigen, a virus comprising an antigen, a

viral particle comprising an antigen, or an antigen, e.g. a polypeptide antigen, which may be free of any other cell-derived or virus-derived material. Cellular fractions may be prepared using methods known to those of skill in the art such as those taught in Cell Biology A Laboratory Handbook (Academic Press 1994 Editor J. E. Celis ISBN 0-12-164715-3)."

The teachings of Hoo are summarized above, however he does not teach the claimed Glycine-Serine linker of claims 79 and 80.

The teachings of Erbe et al. are discussed above.

The teachings of Cantrell et al. are discussed above.

Guillett et al. teach linking of a cytokine, cardiotrophin-like cytokine (CLC), with a recombinant neurotrophic factor (CNTF) receptor via a Glycine-Serine linker $(G_4S)_2$. Guillett et al. observed an increase in stability among the chimeric complex.

Robinson et al. teach the identification of an ideal Glycine-Serine linker length and composition for the Arc repressor dimer. Robinson et al. discuss that identifying a linker, which improves desired properties (i.e. flexibility, stability, increased *in vivo* half-life) of a protein complex would prove to be a very important discovery. Through their random Arc-linker-Arc constructs, Robinson et al. identified an ideal linker with 7 serines and 9 glycines.

It would have been obvious to one of ordinary skill in the art to modify the methods taught by Hoo (and evidenced by Erbe et al. and Cantrell et al.) in order to use a Gly-Ser based linker in forming the fusion polypeptide. One would have been motivated to do so, given the suggestion by Hoo that the method be used to produce a fusion protein comprising a cell membrane binding protein to a cytokine through linkage domain.

There would have been a reasonable expectation of success, given the knowledge that the stability of a cytokine-heterologous protein chimera improved by a 10-mer linker of Glycine-Serine and in the case of a recombinant repressor which is stabilized by a 16-mer Glycine-Serine linker, as taught by Guillett et al. and Robinson et al., respectively. Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Summary

No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BENJAMIN P. BLUMEL whose telephone number is (571)272-4960. The examiner can normally be reached on M-F, 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-1600. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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